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Effects of Anxiolytic Drugs in Animal Models of Multiple Sclerosis

Silvia Novío, Manuel Freire-Garabal and María Jesús Núñez-Iglesias
Lennart Levi Stress and Neuroimmunology Laboratory,
University of Santiago de Compostela
Spain

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS), affecting more than 2 million people worldwide (Hirtz et al., 2007; McQualter & Bernard, 2007; Sospedra & Martin, 2005). Although it has been described for over two hundred years, it is not well characterized and no cure exists (Hirtz et al., 2007; McQualter & Bernard, 2007). For this reason, nowadays there is still considerable interest in the investigation of the pathogenesis of this disease, the improvement of diagnosis, the assessment of prognosis, and the discovery of new therapeutic agents.

The CNS cannot easily be sampled, so to gain ideas about neuroinflammatory diseases, animal models are developed. Experimental research has been performed in many species, including monkeys (Genain & Hauser, 2001), however most of the studies use rodents, fundamentally mice (Campbell et al., 2001; Chandler et al., 2002; Dowdell et al., 1999; Johnson et al., 2004, 2006; Meagher et al., 2007; Mi et al., 2004, 2006; Sieve et al., 2004, 2006; Steelman et al., 2009, 2010; Welsh et al., 2004; Whitacre et al., 1998; Young et al., 2008, 2010) and rats (Anane et al., 2003; Bukilica et al., 1991; Correa et al., 1998; Dimitrijević et al., 1994; Griffin et al., 1993; Kuroda et al., 1994; Laban et al., 1995a, 1995b; Le Page et al., 1994, 1996; Levine et al., 1962; Núñez-Iglesias et al., 2010; Owhashi et al., 1997; Pérez-Nievas et al., 2010; Teunis et al., 2002; Whitacre et al., 1998). In these studies, similar clinical phenotypes are achieved via different routes, so it is probable that some heterogeneity exists in the pathways leading to MS. In general, the standard experimental models of MS include: myelin mutant models, toxic demyelination models, viral models, and autoimmune models, being the virus-induced and immune-mediated models the most common ones for MS.

a. **Myelin mutant models.** Myelin mutants, such as the taiep rat and the *Shiverer* mouse (myelin basic protein (MBP) mutant), as well as gene knockout animals (e.g. myelin associated glycoprotein (MAG) knockout mouse) show axonal degeneration, altered neurotransmission, and in some instances clinical disease (Loers et al., 2004). Myelin mutant models have largely been used to study mechanisms of demyelination and remyelination. However, their relatively high cost has limited their widespread application (e.g. as preclinical drug screening tools).

b. **Toxic demyelination models.** Neurotoxicants such as lysolecithin, ethidium bromide or cuprizone are used to induce chemical lesions. In lysolecithin and ethidium bromide models, a focal lesion is induced by stereotactic injection of the compound into the rodent CNS. The toxic effect of lysolecithin is considered to be selective on myelin producing cells while ethidium bromide is toxic for all nucleolus containing cells (Woodruff & Franklin, 1999). The cuprizone model is widely used to study toxin induced demyelination. In this model, animals are fed with the copper chelator cuprizone (bis-cyclohexanone oxaldihydrazone) leading to demyelination, which is reversed after cessation of the toxin. This model is reliable and has the advantage of good reproducibility regarding the amount and site of demyelination (Matsushima & Morell, 2001).

c. **Viral models**. Several viruses, including Semliki Forest Virus and Theiler's Murine Encephalomyelitis Virus (TMEV), induce disease by neurotrophic infection of the CNS, specifically oligodendrocytes. Succinctly, virally-infected cells are attacked by T cells inducing important humoral responses, which finally lead to demyelination (Ercolini & Miller, 2006; Lavi & Constantinescu, 2005). The Picornavirus TMEV is a naturally occurring pathogen that was originally isolated from mice. In this species, strains of Theiler's virus (BeAn, DA, WW, Yale) cause a biphasic disease that includes an acute CNS inflammatory phase followed by a chronic neuroinflammatory/autoimmune demyelination phase with glial and microglial infection (Oleszak et al., 2004). The chronic phase of the disease has many similarities, both behaviorally and physiologically with progressive MS (Dal Canto et al., 1995; Lipton, 1975; Oleszak et al., 2004; Tsunoda & Fujinami, 1996), so Theiler's virus-induced demyelination (TVID) is commonly used as an excellent animal model of MS (Dal Canto et al., 1995; Oleszak et al., 2004; Tsunoda & Fujinami, 1996) for studying: the pathogenesis, the disease susceptibility factors, the mechanisms of viral persistence within the CNS, and the mechanisms of virus-induced autoimmune disease (Welsh et al., 2009).

d. **Autoimmune models**. Experimental autoimmune encephalomyelitis (EAE) has received the most attention as a model of MS. Clinical and histological features of MS can be actively or passively induced. Active EAE is accomplished through inoculation with spinal cord homogenate or with many different CNS proteins or peptides (such as myelin oligodendrocyte glycoprotein (MOG), myelin-associated oligodendrocyte basic protein (MOBP), oligodendrocyte-specific protein (OSP), proteolipid protein (PLP), and MBP) emulsified in adjuvant (e.g. complete Freund´s adjuvant (CFA), Pertussis toxin, alum, etc) (Tsunoda & Fujinami, 1996). Adjuvants potentiate immune reactions (Lavi & Constantinescu, 2005), ensure persistence of antigens at relevant sites (Lavi & Constantinescu, 2005), and influence stress response pathways inducing changes in levels of hormones such as ACTH (Selgas et al., 1997), so they can modulate the clinical course of EAE (Libbey & Fujinami, 2011). On the other hand, passive EAE is induced through adoptive transfer of myelin specific T cells into naïve animals (Tsunoda & Fujinami, 1996). Both models of EAE induction have been used extensively, with the active model most useful for studying the parameters involved in the initiation of EAE, and the passive model generally used in the study of the effector phase of EAE (Dittel et al., 1999). EAE is polygenic and the susceptibility and the clinical course (acute relapsing, chronic relapsing, relapsing-remitting, chronic progressive) can vary depending on the chosen EAE model and the strain/species of animal being investigated (Lavi & Constantinescu, 2005; Libbey & Fujinami, 2011; T. Owens, 2006).

Therefore, EAE is not a single model, but a number of models that have varying degrees of similarity to MS (Lavi & Constantinescu, 2005).

Some authors have doubts about the validity of experimental models of MS. However, at present it is accepted that although the preclinical research in MS is merely exploratory, it is also very necessary because it has contributed to elucidating key targets in the pathogenesis of MS. They have helped in the discovery of numerous cytokines and chemokines and the characterization of T helper cell subsets, thus playing a key role in understanding basic principles of immune function and autoimmunity (Gold et al., 2006). On the other hand, diagnostic, prognostic, and therapeutic aspects of MS have been cleared and resolved by means of experimental models (Pahan, 2010; Steinman & Zamvil, 2006). In this way, studies on EAE have culminated in three MS therapies (Steinman & Zamvil, 2006). For example glatiramer acetate, which was approved in 1996 for treatment of relapsing-remitting MS, currently is one of the most popular medications for treatment of relapsing-remitting MS, and more than 100,000 individuals with MS worldwide have received glatiramer acetate treatment (Sela, 2006). Besides, nowadays one of the exciting directions in the development of therapy for MS is consideration of various combinations of medications, and once again EAE models have demonstrated to be a valuable tool. They have shown potential synergies between drugs (statins and glatiramer), which show efficacy when used at doses that are suboptimal for these drugs when used alone (Greenwood et al., 2006; Stüve et al., 2006).

2. Stress and multiple sclerosis

The etiology of MS remains unknown, but studies have implicated both genetic and environmental factors (Noseworthy et al., 2000; Sospedra & Martin, 2005). The notion that psychological stress may be related to MS dates back to the time of Charcot, who suggested that the onset of MS is often preceded by grief or vexation, as well as by other socially undesirable circumstances (Charcot, 1877). Many studies since then have found that MS patients, as compared to healthy people or patients with other neurological disorders, report more stressful experiences prior to initial symptomatology. In the 1980s, two controlled studies were published on this issue. Their results showed that MS patients experienced remarkable life stress more frequently than the control subjects in the year (or six months) prior to MS onset (Grant et al., 1989; Warren et al., 1982). In addition to MS onset, relapses have also been found associated with stressful events (Ackerman et al., 2002; Brown et al., 2005, 2006; Franklin et al., 1988; Golan et al., 2008; Grant et al., 1989; Li et al., 2004; Mohr et al., 2004; Sibley, 1997). Franklin et al. (1988) in a longitudinal prospective study on 55 MS patients, with a clinical evaluation every 4 months for about 2 years, found that patients who reported significant negative or stressful life events were 3.7-times more likely to have an exacerbation than those free of such events. Sibley (1997) also found a significant association (p<0.02) between conjugal or job stress and MS relapses; in the same way that Mohr et al. (2004) in a systematic meta-analysis of 14 prospective studies, published from 1965 to 2003, found that there was a significantly increased risk of exacerbation associated with stressful life events (effect size of d=0.53; C.I.=0.40 to 0.65). In line with previously related studies, this relation has been further cleared by imaging techniques (magnetic resonance imaging) with the marker of acute focal brain inflammation, gadolinium (Goodin et al., 1999). In this way, Mohr et al. (2000) studied a group of 36 MS patients, finding that the occurrence of stressful life events was associated with a significantly increased risk of

new gadolinium-enhancing (Gd+) brain lesions. Taken together, these findings and similar observations discovered in animal investigations (Campbell et al., 2001; Chandler et al., 2002; Johnson et al., 2004; Laban et al., 1995a; Meagher et al., 2007; Mi et al., 2004, 2006; Núñez-Iglesias et al., 2010; Pérez-Nievas et al., 2010; Sieve et al., 2004, 2006; Steelman et al., 2009, 2010; Teunis et al., 2002; Welsh et al., 2004; Young et al., 2008, 2010) confirm the necessity of applying preventive and tailored interventions, behavioral and pharmacological, in stressed patients with MS (Golan et al., 2008).

Despite all studies previously commented, some researchers have doubted about the association between the occurrence of stressful life events and the subsequent development of MS disease activity. Pratt (1951) and Gasperini et al. (1995) have not found significant differences between MS patients and control subjects, as far as their experienced stressful events were concerned; and even Nisipeanu and Korczyn (1993) have suggested that psychological stressors could have a "protective effect". Initially it was said that this discrepancy might be the result of a number of research design problems, including infrequent monitoring of patients, small patient samples, subjective reporting bias, type of statistical analysis used, lack of adequate controls, etc (Golan et al., 2008; Goodin, 2008; Martinelli, 2000). However, nowadays it is accepted that the relationship between MS and stressful life events is complex (Brown et al., 2005; Mohr et al., 2000). The type, the timing, and duration of the stressor as well as the animal strain and sex, and the chosen experimental model of MS (Mohr et al., 2004) are factors which determine the result:

a. **Type** (Table 1): Johnson et al. (2004) observed that if social stress is applied concurrently with Theiler's virus infection, disease severity is reduced compared to infected, non-stressed animals. In contrast, if restraint stress is applied concurrent with infection, the disease is again exacerbated (Campbell et al., 2001; Sieve et al., 2004). Likewise, Bukilica et al. (1991) indicated that whereas 19 daily sessions of inescapable tail-shock (80, 5 s, 1 mA) have no effect when administered prior to EAE induction, stressor exposure following EAE induction has a protective effect. Specifically, tail-shock reduces the incidence and duration of EAE, delays disease onset, and decreases the severity of clinical and histological symptoms.
b. **Timing and duration** (Table 1): Repeated moderate stressors suppress clinical signs when they are given before EAE induction, whereas acute severe stressors enhance the progression of disease after its induction (Heesen et al., 2007). Alternatively, acute stress applied prior to induction of EAE increases the severity of the disease (Teunis et al., 2002), and the contrary (i.e. a protective effect) is observed if the stressor is chronic (Levine & Saltzman, 1987; Levine et al., 1962; Whitacre et al., 1998).
c. **Animal strain** (Table 1): Certain inbred mouse strains, including SJL and DBA/2, are very susceptible to persistent CNS infection with TMEV and to the development of TVID, whereas other strains are intermediately susceptible (C3H, AKR, and CBA), and others are still able to clear the virus from the CNS, being resistant to the demyelinating phase of the disease (BALB/c and C57BL/6) (Sieve et al., 2004, 2006; Welsh et al., 1990). For example, Sieve et al. (2004, 2006) have observed important differences between CBA and SJL mice. Concretely: first, SJL mice show symptoms of the chronic phase of disease earlier (at 35 days pi) than CBA mice (at 150 days pi); second, SJL mice gradually develop late disease, whereas CBA mice have a sudden onset of severe symptoms; third, the incidence of the chronic phase is higher in SJL than in CBA mice (100% of the

Study	Model of MS	Stressor characteristics (type, timing, and duration)	Results	
			Acute stressor*	Chronic stressor**
Pérez-Nievas et al., 2010	DA rats, EAE (MOG/CFA)	Restraint stress started the same day of induction. Duration: 12d or 21d		Exacerbation (12d) Protective (21d)
Núñez-Iglesias et al., 2010	Lewis rats, EAE (MBP/CFA)	Noise stress started 5d prior to induction. Duration: 19d or 39d		Exacerbation (19d or 39d)
Young et al., 2010	SJL/JCrHsd mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 28d		Exacerbation
Steelman et al., 2010	C57BL/6 mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 7d or 4w		---
Steelman et al., 2009	SJL mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 8d		Exacerbation
Young et al., 2008	CBA mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 4w		Exacerbation
Meagher et al., 2007	Balb/cJ mice, Theiler (BeAn strain)	Social disruption stress started 1w before infection. Duration: 7d		Exacerbation
Mi et al., 2004, 2006	CBA mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 2 or 7 d	Exacerbation	Exacerbation
Sieve et al., 2006	CBA mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 4w		Exacerbation
Johnson et al., 2004	Balb/cJ mice, Theiler (BeAn strain)	Social disruption stress started: * 1w prior to infection or * the day of infection Duration: 7d		Exacerbation (stress applied prior to infection) Protective (stress applied concurrent with infection)
Sieve et al., 2004	SJL mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 4w		Exacerbation
Welsh et al., 2004	CBA mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 4w		Exacerbation
Anane et al., 2003	Lewis rats, EAE (MBP/CFA)	Physical stress (microwaves) started the day of induction. Duration: 21d		---
Chandler et al., 2002	SJL/J mice, EAE (PLP/CFA)	Restraint stress was performed on days 2 and 3 post-induction. Duration: 2d	Exacerbation	

Study	Model of MS	Stressor characteristics (type, timing, and duration)	Results	
			Acute stressor*	Chronic stressor**
Teunis et al., 2002	Wistar rats, EAE (MBP/CFA)	Neonatal maternal deprivation was performed aprox. 7w before induction. Duration: 24h	Exacerbation	
Campbell et al., 2001	CBA mice, Theiler (BeAn strain)	Restraint stress started the day prior to infection. Duration: 4w		Exacerbation
Dowdell et al., 1999	B10.PL mice, EAE (MBP/CFA)	Restraint stress started the day prior to induction. Duration: 21d		Protective
Whitacre et al., 1998	Lewis rats, EAE (MBP/CFA)	Restraint stress started 5 days prior to induction. Duration: 23d		Protective (9h of stress/d) Exacerbation (1 or 12h of stress/d)
Correa et al., 1998	Wistar rats, EAE (MBP/CFA)	Varied stress (swimming, predator odor, water deprivation, crowding, restraint, high-intensity sound, and cage inclination) was performed for the 14d before or after induction. Duration: 2w		Protective (stress before induction) Exacerbation (stress after induction)
Owhashi et al., 1997	Lewis rats, EAE (MBP/CFA)	Water bath (44ºC) was performed for the 10 or 13d before or after the induction. Duration: 10 or 13d	--- (stress before induction) Protective (stress after induction)	
Le Page et al., 1996	Lewis rats, adoptive EAE	Physical exercise was performed the 2d before or after the adoptive transfer of EAE. Duration: 2d	--- (stress before induction) Scantily protective (stress after induction)	
Laban et al., 1995a	DA rats, EAE (SCH/CFA)	Neonatal handling or gentling was performed 8w before induction. Duration: 4w	Exacerbation	
Laban et al., 1995b	DA rats, EAE (SCH/CFA)	Maternal deprivation was performed 8w before induction. Duration: 28d Early weaning was performed for 5-6w before induction. Duration: 1-2w		Protective (maternal deprivation Exacerbation (early weaning)

Study	Model of MS	Stressor characteristics (type, timing, and duration)	Results	
			Acute stressor*	Chronic stressor**
Le Page et al., 1994	Lewis rats, EAE (SCH/CFA)	Physical exercise was performed for the 10 days after induction. Duration: 10d		Protective
Dimitrijević et al., 1994	Lewis and DA rats, EAE (SCH/CFA)	Neonatal sound stress was performed 2 or 3w before induction. Duration: 1h	Exacerbation (Lewis) Protective (DA)	
Kuroda et al., 1994	Lewis rats, EAE (SCH/CFA)	Restraint stress was performed 1 or 8d after induction. Duration: 3d	--- (1d) Protective (8d)	
Griffin et al., 1993	Lewis rats, EAE (MBP/CFA)	Restraint stress started 5d before induction. Duration: 23d		Protective
Bukilica et al., 1991	DA rats, EAE (SCH/CFA)	Electric stress or sound stress was performed the 19d before or after induction. Duration: 19d		Protective (electric stress after induction and sound stress) --- (electric stress before induction)

Table 1. Animal studies (published from 1991 to 2010) on the effects of stress on disease manifestation. Studies are classified according to the type of stressor used: acute or chronic. *Acute stressor, stressor lasting less than 1 h and for less than 5 days; **chronic stressor, stressor lasting longer than 1 h and more than 5 days (although in most instances they were not presented all through the day). Abbreviations. CFA, complete Freund's adjuvant; d, day; DA, Dark August; EAE, experimental autoimmune encephalomyelitis; h, hour; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; PLP, proteolipid protein; SCH, spinal cord homogenate; w, week.

SJL mice develop severe symptoms of the chronic phase of the disease, versus to 70% (at most) of the CBA mice) (Friedmann & Lorch, 1985; Oleszak et al., 2004; Simas & Fazakerley, 1996). Susceptibility to TMEV persistence and TVID has been linked to genetic differences between strains of mice (Bureau et al., 1993; Monteyne et al., 1997; Oleszak et al., 2004; Rodriguez et al., 1990), which could explain the variability in their responsivity to stress and their different immunological background. In relation to EAE, it has also been shown that the susceptibility varies depending on the strain. So, whereas ABH and SJL mice develop relapsing EAE to disease induced by whole myelin, C57BL/6 mice are resistant (Lavi & Constantinescu, 2005).

d. **Sex**: A very discussed topic has been the sex impact in the disease process (Hill et al., 1998; Kappel et al., 1990; Lipton, 1975; Sieve et al., 2004, 2006). In some studies, female SJL mice are known to have greater susceptibility to disease as compared to males, a pattern that is similar to that found in human MS patients (Hill et al., 1998; Kappel et al., 1990; Sieve et al., 2004); on the contrary, other studies indicate that male mice develop more severe symptomatology of disease than females (Alley et al., 2003). It has been suggested that these apparently contradictory results may be due to different study

designs and criteria used such as housing conditions or strain of Theiler's virus (Sieve et al., 2004). However, the sexual dimorphism of the immune system, the stress systems or the bidirectional communication between the reproductive system and the stress systems are reasons which may also explain, at least in part, this discrepancy (Gaillard & Spinedi, 1998; Whitacre et al., 1999). On the other hand, it is important to emphasize that the pattern of sex differences found can be complex. Sometimes, there are no sex differences in the early viral infection, existing on the contrary, greater behavioral signs in males than in females in later disease (Sieve et al., 2004).

e. **Experimental model of MS** (Table 1): Several authors have observed that stress exacerbates the early viral infection (Campbell et al., 2001; Sieve et al., 2004) and the later demyelinating disease (Sieve et al., 2004) in Theiler's virus infection. However, this does not coincide with studies using EAE, which show no effect of stress prior to disease induction, and a suppression during disease induction (Bukilica et al., 1991; Dowdell et al., 1999; Griffin et al., 1993; Levine & Saltzman, 1987; Levine et al., 1962). The differences in how stress affects EAE and Theiler's virus infection may lie in their immunological mechanisms of demyelination and neuronal destruction. However, the observed discrepancy between these two experimental models of MS can also be attributed to the fact that the stressor is applied during different phases in the immunological response of the disease process (Sieve et al., 2004).

3. Effects and mechanisms of action of benzodiazepines on models of MS

Benzodiazepines (alone or in association with other therapies) have long been used to relieve or resolve symptoms and signs associated with MS (Arroyo et al., 2011; Bush et al., 1996; D'Aleo et al., 2011; Hung & Huang, 2007; Meythaler et al., 1991; Rode et al., 2003; Solaro et al., 2010; Stork & Hoffman, 1994; Velez et al., 2003; Yerdelen et al., 2008). For example, Hung and Huang (2007) have observed that a combination of lorazepam and diazepam may be considered to release catatonic features in patients with MS, although the prescription of benzodiazepines associated with electroconvulsive therapy is another therapeutic option commonly used (Bush et al., 1996; Hung & Huang, 2007). Likewise, painful spasms, tremors or seizures (with or without associated anxiety symptoms) are treated with benzodiazepines such as clonazepam (Rode et al., 2003; Yerdelen et al., 2008), diazepam (D'Aleo et al., 2011; Meythaler et al., 1991; Rode et al., 2003) or tetrazepam (Rode et al., 2003); and even, Velez et al. (2003) have observed that patients with dramatic opisthotonic posturing and vermiform tongue fasciculations respond well to intravenous doses of lorazepam.

Benzodiazepines are used clinically as tranquilizers, muscle relaxants, anticonvulsants, anxiolytics, and sedative-hypnotics. These effects are mediated primarily via the central benzodiazepine receptors (CBR) located in the CNS (Heiss & Herholz, 2006); however, in addition to binding of $GABA_A$ receptors in the CNS, benzodiazepines bind to another site in peripheral tissues. This second type of recognition sites was mistakenly termed "peripheral benzodiazepine receptor" (PBR) for many years (Table 2). However, at present scientists prefer using the nomenclature: translocator protein (18 kDa) (TSPO) (Papadopoulos et al., 2006a). The TSPO is different from the CBR in terms of function, structure, expression, and pharmacological action (Gavish et al., 1999; Woods & Williams, 1996), so their study must be performed separately.

3.1 Effects mediated by the CBR

To date, only one study has been conducted to examine the influence of central benzodiazepine agonists on the development of animal models of MS (Núñez-Iglesias et al., 2010). Núñez-Iglesias et al. (2010) have observed that alprazolam decreases the clinical (paralysis, paraplegia, piloerection, etc) and histological (perivascular inflammatory infiltrate) manifestations of acute EAE in Lewis rats exposed to a chronic auditory stressor.

The molecular mechanisms mediating the clinical effects of central benzodiazepines in animal models of MS are unknown. However, it is thought that stress response mediators might play an important role in them.

	CBR	**TSPO**
Structure	Part of a macromolecular complex that also contains a γ-aminobutyric acid ($GABA_A$) receptor site and a chloride ion channel (Heiss & Herholz, 2006).	Part of a hetero-oligomeric complex comprised of the voltage-dependent anion channel and an adenine nucleotide carrier (McEnery et al., 1992; Papadopoulos et al., 2006a).
Subcellular localization	Plasma membrane of neurons (Heiss & Herholz, 2006).	Mitochondrial outer membrane (Gavish et al., 1999; Heiss & Herholz, 2006). Nonmitochondrial localization: plasma membrane (Gavish et al., 1999; Olson et al., 1988), nucleus, and perinuclear area (Gavish et al., 1999; Kuhlmann & Guilarte, 2000).
Localization	**Central**: medial occipital cortex, cerebellum, thalamus, striatum, pons (Heiss & Herholz, 2006).	**Peripheral**: kidney (Gavish et al., 1999), lung (Gavish et al., 1999), skeletal muscle (Gavish et al., 1999), liver (Gavish et al., 1999), heart (Gavish et al., 1999), uterus (Gavish et al., 1999), testis (Gavish et al., 1999), ovaries (Cosenza-Nashat et al., 2009; Gavish et al., 1999), haematogenous cells (Cosenza-Nashat et al., 2009; Olson et al., 1988; Ruff et al., 1985), and the steroid hormone-producing cells of the adrenal cortex (Gavish et al., 1999). **Central** (low concentrations): principally non-neuronal cells: ependymal lining of the ventricles, choroid plexus (Mattner et al., 2005), and glial cells (astrocytes and microglia) (Cosenza-Nashat et al., 2009; Mattner et al., 2005). Some studies also suggest that neurons may express TSPO (Jayakumar et al., 2002).

Table 2. Benzodiazepine binding sites. Main differences between CBR (central benzodiazepine receptor) and TSPO (translocator protein (18 kDa), also known as: peripheral-type benzodiazepine binding site, peripheral benzodiazepine receptor or mitochondrial benzodiazepine receptor).

3.1.1 Psychoneuroimmunoendocrinology and MS

Stress affects host defenses comprising neuronal, endocrine, and immune reactions. This complex network of bi-directional signals plays a vital role in determining the outcome of the stress response, since when the balance among these systems is altered, the risk of disease increases (Masood et al., 2003).

Figure 1 shows how stress impairs both natural and specific immune responses, which could influence morbidity associated with MS. Changes in the absolute number of lymphocytes, T-lymphocytes, T-helper, and T-suppressor cells have been reported (Freire-Garabal et al., 1991, 1997). Stress also interferes with several immune responses such as splenic cytotoxic activities, mediated by NK cells and cytotoxic T lymphocytes (Núñez et al., 2006), the activity of phagocytosis (Freire-Garabal et al., 1993a, 1993b), the delayed type hypersensitivity (DTH) response (Freire-Garabal et al., 1997; Núñez et al., 1998; Varela-Patiño et al., 1994), the blastogenic response of spleen lymphoid cells (Freire-Garabal et al., 1991, 1997), and T-dependent antibody responses (Fukui et al., 1997).

Research into the mechanisms by which the stressors are translated into impaired immune function and vulnerability to disease has focused primarily on two pathways: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic branch of the autonomic nervous system (ANS) (Figure 1). Whereas increased sympathetic adrenal activity appears to play a major role in immune changes observed after acute stress, HPA axis-activity together with sympathetic mechanisms are mainly responsible for the inhibition of cellular and humoral immune responses following chronic stress exposure (Glaser & Kiecolt-Glaser, 2005). The importance of these systems is so high that when neuroendocrine hyper- or hypoactive responses of the HPA axis or the sympathetic nervous system (SNS) to stress occur, they function as risk factors of specific diseases, such as neurodegenerative diseases. Concretely, Gold et al. (2005) highlight the relevance of the functional status of the HPA axis in the control of EAE. During the experimentally induced disease in animals, the endogenous levels of glucocorticoids are elevated and the recovery from the disease is clearly dependent on this endocrine change (MacPhee et al., 1989). This endocrine response is immunologically mediated so it is mainly the result of the stimulation of the HPA axis by cytokines (such as IL-1) produced during the immune response that induces the autoimmune disease (Del Rey et al., 1998). In EAE models, the negative feedback system mediated via the glucocorticoid receptors seems to be disturbed (Gold et al., 2005), with the stressors favoring the perpetuation of this disregulation, as is shown by increased corticosterone levels in stressed rats relative to unstressed animals (Núñez-Iglesias et al., 2010). The importance of an increased HPA axis activity is supported by the observation that this phenomenon is related to the clinical disease course (Then Bergh et al., 1999).

The most basic literature regarding the HPA axis in pharmacology studies has been obtained in rats. More recently the mouse has been used due to the availability of genetically manipulated mice. The mouse is a model species of choice for genetic engineering because: a) its genes have an equivalent in humans; b) its genome is easy to modify by homologous recombination; c) it allows the creation of relevant animal models of human disease; d) numerous biological and biochemical functions of the mouse are similar to those of humans; e) it is easy to breed, less expensive to feed than rats and lives in smaller cages. These genetic models have allowed the determination of genes involved in anatomic and

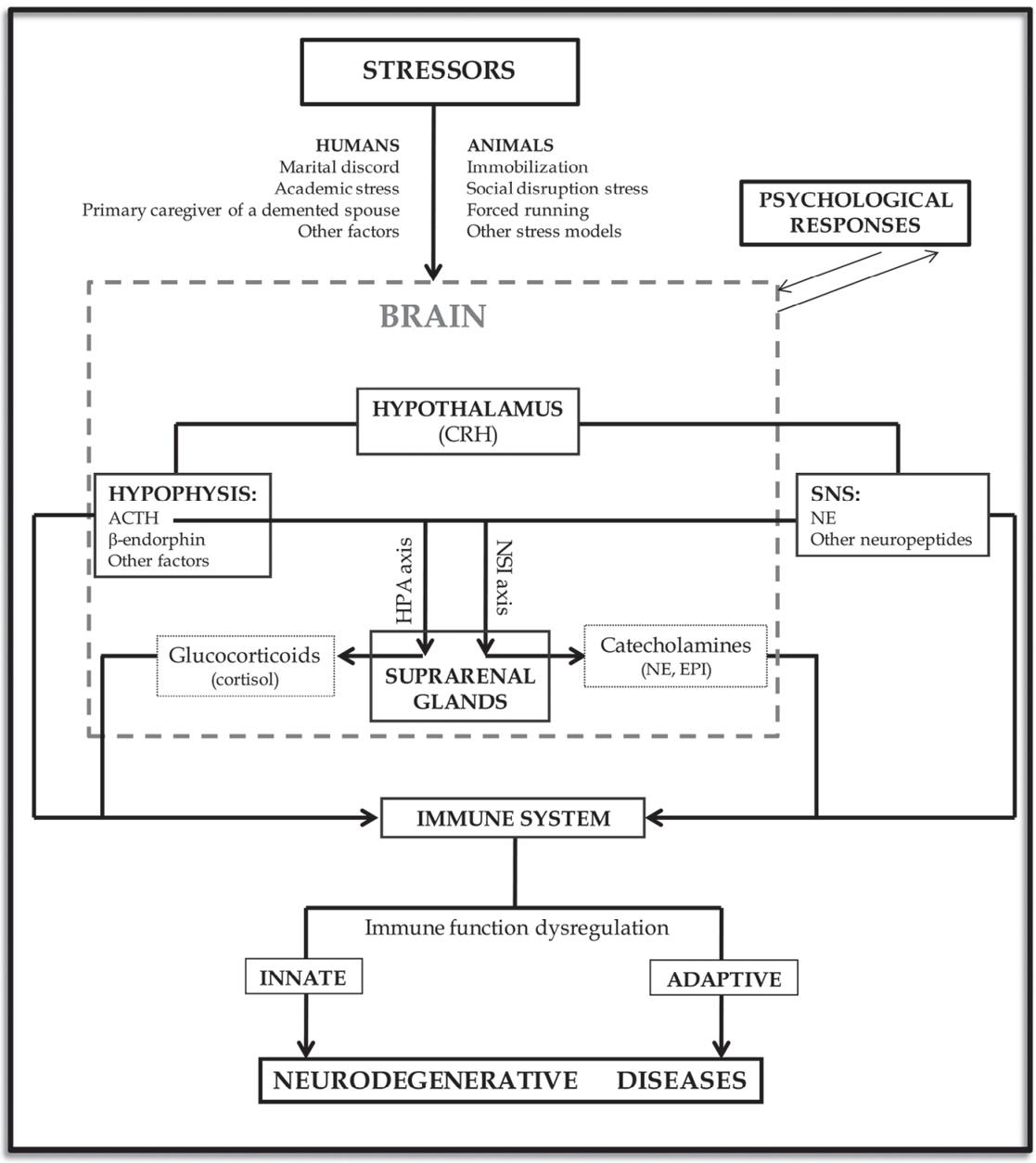

Fig. 1. Biological pathways mediating stress-induced modulation of immune function. The hypothalamic-pituitary-adrenal (HPA) axis and the neocortical-sympathetic-immune (NSI) axis are the main neural efferent pathways through which stress can affect the activity of the immune system. Stress-induced impairments in immunity can influence morbidity associated with neurodegenerative diseases. Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; EPI, epinephrine; NE, norepinephrine; SNS, sympathetic nervous system. Own production. Source: Friedman & Lawrence (2002) and Godbout & Glaser (2006).

functional alterations of brain circuits critical for stress regulation. Furthermore, they have contributed to understanding genetic vulnerability to anxiety and its pharmacological treatment (Gardier et al., 2009).

3.1.2 Benzodiazepines for control of stress associated with MS

Several mechanisms could explain the effects mediated by central benzodiazepines on attenuated manifestations of MS:

a. Inhibitory influence on the activity of the HPA axis.

GABA and benzodiazepines reduce levels of HPA axis hormones, including CRF (corticotropin releasing hormone) and ACTH (adrenocorticotropic hormone) and corticosterone (Arvat et al., 2002; Bizzi et al., 1984; M.J. Owens et al., 1989) acting on CBR. Central pharmacological effects related to CBR acting by facilitating inhibitory GABA neurotransmission in the CNS, may regulate the release of neuroendocrine hormones involved in the immune response to stress.

b. Platelet activating factor (PAF) antagonist properties.

Activation and control of the coagulation cascade, modulated by antigen-specific mediators of cellular immunity, appear to be of prime importance in the animal models of MS (Inoue et al., 1996). Susceptibility and resistance to EAE in rodents correlate with the induction of procoagulant and anticoagulant activities. Geczy et al. (1984) observed that anticoagulants produced by cells from nonsusceptible EAE rodents suppressed the common coagulation pathway by inhibiting trombin and factor Xa activities.

Central benzodiazepines such as alprazolam have PAF antagonist properties. It was found that in washed human platelets the alprazolam potently inhibits PAF-induced changes in shape, aggregation, and secretion, with the effects being specific for PAF activation (Kornecki et al., 1984). Likewise, Ng and Wong (1988) also showed that alprazolam can inhibit the [^{3}H]PAF binding to the human peripheral blood mononuclear leukocytes. In this context, it is interesting to point out that PAF plays a role in the activation of the HPA axis and glucocorticoid secretion and can serve as a mediator in the interactions of the immune system with the CNS. Concretely, PAF is an activator of the HPA axis in the rat. Its activation, which causes significant stimulation of hypothalamic CRH, pituitary ACTH, and adrenal corticosterone secretion, is inhibited by alprazolam. In addition, the PAF stimulates ACTH secretion by dispersed rat pituicytes, which is also inhibited by the alprazolam (Bernardini et al., 1989). The specific antagonism of PAF action by psychotropic drugs suggests that PAF or PAF-like phospholipids may play a role in neuronal function (Kornecki et al., 1987).

c. Inhibitory activity on proinflammatory cytokines.

Besides the mechanisms previously described, downstream effects of the alprazolam on immunological and inflammatory parameters important for EAE must be underscored. Secondarily recruited inflammatory cells account for the vast majority of infiltrating cells in MS lesions and they play a pivotal role in CNS tissue damage (Ransohoff, 1999). The detailed mechanisms by which inflammatory cells enter the CNS compartment are not completely understood. However, evidence suggests that cytokines are essential for

this process (Karpus & Ransohoff, 1998). Enhanced expression of proinflammatory cytokines in the CNS, such as the monocyte chemoattractant protein 1 (MCP-1), has been demonstrated both in animal models of MS (Juedes et al., 2000) and in human case series (D'Aversa et al., 2002), and Karpus et al. (1997) have showed that the severity of manifestations is reduced by anti-MCP-1 antibodies. Additionally, mice that lack C-C chemokine receptor 2 (CCR2), the major receptor on monocytes for MCP-1, fail to develop the disease after active immunization (Fife et al., 2000) and are resistant to induction of it by the adoptive transfer of primed T cells from syngenic wild-type mice (Izikson et al., 2000). The effect of alprazolam on the expression levels of cytokines has been studied (Chang et al., 1992; Oda et al., 2002). Oda et al. (2002) have noted a potent inhibitory activity of this benzodiazepine on IL-1α-elicited MCP-1 production in T98G cells. Likewise, alprazolam inhibits the production of cytokines IL-1β and MCP-1 in LPS-stimulated mouse macrophage cells (Oda et al., 2002) and reduces the production of IL-2 by murine splenic T-cells (Chang et al., 1992). These findings suggest that alprazolam might prevent the infiltration of specific regions by an excess of proinflammatory cytokines. Since the excess production of proinflammatory cytokines exacerbates MS or EAE (Karpus & Ransohoff, 1998), the above-described action of alprazolam might explain the improvement of manifestations associated with EAE in non-human species or patients treated with this drug.

3.2 Effects mediated by the TSPO

Microglia play a significant role in the pathogenesis of MS (Venneti et al., 2006). They serve housekeeping functions and maintain homeostasis of local environments (Davalos et al., 2005; Nimmerjahn et al., 2005). In response to CNS insults, microglia change from a resting to an activated state to function as phagocytic macrophages (Chan et al., 2003; Fetler & Amigorena, 2005). This transition of microglia into an activated state includes a change in their morphology, migration towards the site of neuronal damage, proliferation until they quadruplicate in number (Davalos et al., 2005; Fetler & Amigorena, 2005), overexpression of cell markers (Agnello et al., 2000; Banati et al., 1997, 2000; Debruyne et al., 2003; Gavish et al., 1999; Kuhlmann & Guilarte, 2000; Versijpt et al., 2005; Vowinckel et al., 1997), and release of a widespread variety of substances or molecules (Chao et al., 1992, 1995a, 1995b; Colton et al., 1993; D'Aversa et al., 2002; Giulian et al., 1986, 1990; Heyes et al., 1996; McManus et al., 1998; Murphy et al., 1995; Righi et al., 1989). These findings demonstrate that microglia (together with perivascular macrophages -Guillemin & Brew, 2004-) represent a first line of the immune defense system of the brain (Davalos et al., 2005; Fetler & Amigorena, 2005; Nimmerjahn et al., 2005), and justify their description as a "sensor for pathological events in the CNS" (Kreutzberg, 1996). Parallel to this protective function, microglia can also contribute to aggravating the underlying neuronal damage via the synthesis and release of neurotoxins (Chao et al., 1992, 1995a; Colton et al., 1993; Giulian et al., 1990; Heyes et al., 1996), cytokines (Chao et al., 1995b; Giulian et al., 1986; Righi et al., 1989), and chemokines (D'Aversa et al., 2002; McManus et al., 1998; Murphy et al., 1995). Taking into account these results, it is concluded that microglia can exist in different states of activation depending on the microenvironment, with some states favoring the secretion of substances damaging neurons and other states favoring a protective phagocytic role (Morgan et al., 2005).

Microglia must maintain the balance between neurotoxicity and neuroprotection in injury, but the complex network of factors which governs their responses is only beginning to be

deciphered (Biber et al., 2007; Glezer et al., 2007). Certainly, it would be interesting if some components of the network of microglial control could be manipulated for prognostic or therapeutic purposes of MS (Rock & Peterson, 2006). In this regard, TSPO plays a very important role. TSPOs are involved in the regulatory processes and metabolic functions of the tissue in which they are present. Outside the CNS: i) it is thought to aid in the transport of cholesterol from the outer to the inner mitochondrial membranes and thus be vital in steroid synthesis (Papadopoulos et al., 1997); ii) as a constituent of the mitochondrial permeability transition pore, TSPO is believed to regulate cell death (McEnery et al., 1992) and mitochondrial respiration (Hirsch et al., 1989); iii) evidence for an immunomodulatory role for this receptor includes the ability to: modulate chemotaxis and phagocytosis in peripheral monocytes and neutrophils (Marino et al., 2001; Ruff et al., 1985), induce cytokine expression and superoxide generation (Zavala et al., 1990), regulate macrophage functions (Pawlikowski, 1993), and stimulate formation of antibody-producing cells (Zavala & Lenfant, 1987), among others (Gavish et al., 1999); iv) TSPO is also thought to play a role in cell proliferation and differentiation (Camins et al., 1995), in protein and ion transport (Casellas et al., 2002; Gavish et al., 1999), and in bile acid synthesis (Lacapère & Papadopoulos, 2003; Woods & Williams, 1996). On the other hand, the functions of this receptor within the CNS are less known. It is suggested that it is involved in neurosteroid synthesis (Papadopoulos et al., 2006b), regulating mitochondrial function (Casellas et al., 2002), and modulating neuroinflammation in microglial cells (Wilms et al., 2003). The fact that TSPO knockout mice die at an early embryonic stage (Papadopoulos et al., 1997) strongly suggests that TSPO is involved in basic cell functions and is essential for embryonic development.

The main findings derived from the study of TSPO in MS patients or animal models of MS are detailed next:

a. TSPO as *in vivo* marker of neuronal damage in MS.

Reactive gliosis based on morphological examination is a microscopic finding in brain tissue sections and can only be obtained from invasive biopsy or postmortem autopsy. Therefore, the development and validation of an *in vivo* biomarker of glial damage is a major advance in the neurology field. In this way, the visualisation of the TSPO has received great importance in MS patients.

TSPO is expressed in the undamaged CNS at only a low level (Agnello et al., 2000; Banati et al., 2000; Gavish et al., 1999); however, its expression is dramatically increased (mainly on microglia and in minor importance on astrocytes) in inflammatory diseases such as MS (Banati et al., 2000; Debruyne et al., 2003; Versijpt et al., 2005; Vowinckel et al., 1997) and animal models of MS (Agnello et al., 2000; Banati et al., 2000; Gavish et al., 1999; Vowinckel et al., 1997). This up-regulation, which reflects an activation of resident microglia, can be visualized and measured using *in vitro* receptor autoradiography and binding assays as well as *in vivo* imaging techniques, such as PET (Maeda et al., 2004). So, in recent years a number of PET ligands with affinity to the TSPO have been developed and tested (e.g. Ro5-4864, PK11195, DAA1106, and vinpocetine) (Junck et al., 1989; Maeda et al., 2004). This has propitiated that nowadays TSPO cellular expression can be considered a reliable biomarker for neuroinflammation and gliosis with neuronal damage (Banati et al., 2000; Debruyne et al., 2003; Mattner et al., 2005; Versijpt et al., 2005; Vowinckel et al., 1997).

b. Neuroprotective function: anti-inflammatory and anti-apoptotic properties.

Recent evidence suggests that TSPO may play an important neuroprotective role in MS patients, both for its anti-inflammatory and its anti-apoptotic properties.

b.1 Anti-inflammatory properties.

Some investigations point to the possibility that the TSPO may participate actively in neuroinflammation and may thus itself be a target for therapeutic intervention. In this way, it has been demonstrated that TSPO ligands (Choi et al., 2002; Ryu et al., 2005) and some benzodiazepines (Wilms et al., 2003) possess anti-inflammatory properties. The PK11195 ligand inhibits increases in cyclooxygenase-2 levels in cultured human microglia (Choi et al., 2002), decreases expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) (Choi et al., 2002; Ryu et al., 2005) and reduces neuronal death in the quinolinic acid–injected rats (Ryu et al., 2005). Likewise, Wilms et al. (2003) have observed that midazolam, clonazepam, and diazepam interfere with the synthesis and release of proinflammatory (TNF-α) and neurotoxic (nitric oxide -NO-) molecules generated by activated microglia *in vitro*. The anti-inflammatory action associated to TSPO is not exclusive for microglial cells, it has also been shown on human blood cells (Bessler et al., 1992; Lenfant et al., 1986; Zavala et al., 1990). It is known that PK11195 and Ro5-4864 inhibit IL-3-like activity secretion in human peripheral blood mononuclear cells, and that IL-2, IL-1, TNF-α, and IL-6 production is inhibited by Ro5-4864 (Bessler et al., 1992; Lenfant et al., 1986). Likewise, treatment of mice with Ro5-4864 markedly reduces the capacity of macrophages to produce key mediators of inflammation such as reactive oxygen intermediates, IL-1, TNF, and IL-6 (Zavala et al., 1990). In particular, TNF is considered an important pharmacological target for the therapy of MS and drugs able to inhibit TNF-synthesis, such as the phosphodiesterase inhibitors, have been reported to ameliorate EAE (Sommer et al., 1995). Taken together, these findings are very promising, specially if we bear in mind that diazepam has been undoubtedly demonstrated to be neuroprotective in experimental models of other diseases (Schwartz-Bloom et al., 2000).

The true meaning of increased TSPO expression in microglia is unknown, however Wilms et al. (2003) have postulated that the presence of a high density of TSPO in human MS might be an adaptive response to neuronal damage with subsequent decreased release of neurotoxic microglial mediators. This hypothesis is supported by findings of Lacor et al. (1999) and Costa et al. (1994). They demonstrated that TSPO density is highly increased after peripheral nerve injury, with TSPO returning to normal levels when regeneration is complete or with TSPO remaining elevated in the absence of regeneration. A possible source of endogenous ligands of TSPO are astrocytes, which release substantial amounts of endozepines (Patte et al., 1999). These findings suggest that TSPO may be a trophic factor in recovery from brain injury.

A lot has been speculated about the mechanisms by which TSPO specific ligands confer protection. However, associations between TSPO activation and stimulation of neurosteroid synthesis have been noted (Lacapère & Papadopoulos, 2003; Le Goascogne et al., 2000). For example, Le Goascogne et al. (2000) have shown that TSPO activation in astrocytes promotes the synthesis of neurosteroids (Le Goascogne et al., 2000), which possess neurotrophic and neuroprotective activity (Le Goascogne et al., 2000) and are

inhibitors of TNF production (Di Santo et al., 1996). A similar increase is obtained with anxiolytic benzodiazepines known to bind to both classes of benzodiazepine receptors (diazepam). On the contrary, ligands selective for the $GABA_A$ receptor (clonazepam) have no effect on steroid synthesis (Papadopoulos et al., 1992). On the other hand, Cascio et al. (2000) have shown a correlation among TSPO expression, steroid synthesis, myelination, and oligodendrocyte differentiation, thus reasserting the trophic function of TSPO in recovery from brain damage.

b.2 Anti-apoptotic properties.

The association of TSPO with the mitochondrial permeability transition pore suggests a role in the regulation of cell survival in microglia (McEnery et al., 1992). The participation of the TSPO in apoptotic processes has been demonstrated neither in MS patients nor in animal models of MS. However, studies that have induced overexpression of TSPO in cells different from those microglial ones suggest its implication in cell death regulation (Carayon et al., 1996; Everett & McFadden, 2001; Johnston et al., 2001; Rey et al., 2000; Stoebner et al., 2001). Interestingly, forced TSPO overexpression in myxoma poxvirus-infected macrophages blocks apoptosis (Everett & McFadden, 2001), in the same way that forced TSPO expression in neurons *in vivo* and Jurkat cells *in vitro* also protects these cells from apoptosis (Johnston et al., 2001; Stoebner et al., 2001). Likewise, it has been shown that TSPO upregulation in testicular Leydig cells (Rey et al., 2000) and in blood phagocytic cells (Carayon et al., 1996) preserves them from cytokine- and oxidant-induced cell death, respectively. TSPO expression in microglia may thus protect them from various toxins, thereby contributing to longer microglia life spans in the brain.

c. Neurotoxic effects.

A wealth of literature suggests that the TSPO overexpression , in addition to playing a protective role, can contribute to tissue destruction and disease progression (Block et al., 2007; Kreutzberg, 1996; Rothwell & Hopkins, 1995). When microglia enter an overactivated state, they synthesize and release a battery of potent neurotoxins (including free radicals (Block et al., 2007; Chao et al., 1995a), NO (Chao et al., 1992), proteinases (Colton et al., 1993), eicosanoids (Heyes et al., 1996), and excitotoxins (Giulian et al., 1990), cytokines (IL-1 (Giulian et al., 1986), IL-6 (Righi et al., 1989), and TNFα (Chao et al., 1995b)), and chemokines (such as MIP-1α (Murphy et al., 1995), MIP-1β (McManus et al., 1998), and MCP-1 (D'Aversa et al., 2002)) that cause neurotoxicity, influencing the viability and function of neurons and exacerbating neuronal injury. Two major possible neurotoxic secretion products of microglial cells are NO and TNF-α (Wilms et al., 2003). NO is neurotoxic due to inhibition of complex 1 and 2 of the respiratory chain. Moreover, it reacts with superoxide anion to generate peroxynitrite, a highly reactive molecule capable of oxidizing proteins, lipids, and DNA. The cytokine TNF-α is an important factor in the regulation of neuronal apoptotic cell death, which is expressed by astrocytes and microglial cells in brain lesions of MS patients (Wilms et al., 2003).

The inhibition of microglial activation by a pharmacological approach, using non-steroidal anti-inflammatory drugs or minocycline, has been hypothesized to reduce neuronal damage in animal models of neurodegenerative diseases (Du et al., 2001). Furthermore, activation of microglia also inhibits neurogenesis in the rat hippocampus,

and hippocampal regeneration is restored by blocking microglial activation with either indomethacin (Monje et al., 2003) or minocycline (Ekdahl et al., 2003). These studies suggest that activation of microglia could perpetrate neurodegeneration through several mechanisms.

4. Conclusion

Animal models of MS are a very beneficial tool, which have led to a better understanding of MS. New clues to the pathogenesis of MS and new potential markers for the diagnosis and prognosis of MS have been gained from research in animal models. Likewise, they have helped in the development of therapeutic approaches that are currently being used.

The susceptibility to MS is modulated by interactions among many factors. In this context, it has been hypothesized that disease onset, progression, and relapses in MS are associated with stressful life events, and this alleged relation has been confirmed by sophisticated medical techniques. However, it is necessary to bear in mind that stressor characteristics are key factors in determining the effects of stress on MS symptom development.

Drugs known to affect the immune system have become the primary focus for managing MS. However, the most recent findings suggest that benzodiazepines might be an add-on option for MS treatment because they can modify the stress-induced manifestations of EAE by interacting with CBRs. Concretely, it has been demonstrated that alprazolam reduces the latent period and inflammatory lesions of the SNC and delays the onset of the disease. Several mechanisms have been hypothesized to explain the effects of this type of drugs, which influence hormonal, immune, endocrine, and/or inflammatory parameters associated with the HPA axis and the sympathetic branch of the ANS.

Recent evidence suggests that TSPOs might play a dual role in MS patients and perform neuroprotective and neurotoxic functions. On the other hand, because TSPO is dramatically up-regulated in MS, TSPO cellular expression is considered a reliable marker for diagnosis of the disease progression and of the therapeutic response.

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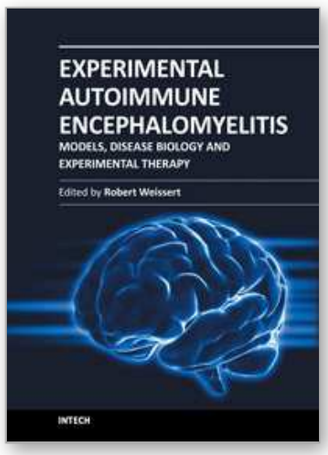

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Experimental Autoimmune Encephalomyelitis - Models, Disease Biology and Experimental Therapy is totally focused on the model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE). The book chapters give a very good and in depth overview about the currently existing and most used EAE models. In addition, chapters dealing with novel experimental therapeutic approaches demonstrate the usefulness of the EAE model for MS research. With an international perspective, this book features contributions from authors throughout the world, Australia, Germany, Japan, Spain, Taiwan, and USA. There is an impressive international Faculty that provides insight into current research themes. This further demonstrates the importance of EAE in research all over the world. The book will provide established researchers and students with novel insights and guidance for their research and will help to push the field forward.

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